Early allergen exposure and atopic eczema

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Summary

Background: The relationship between exposure to indoor aeroallergens in early life and subsequent eczema is unclear. We have previously failed to show any significant associations between early life exposure to house dust mite (*Der p* 1) and cat fur (*Fel d* 1) allergens and either sensitization to these allergens or wheeze. We have also previously reported *lower* prevalence of parentally-reported doctor diagnosed eczema by age two for children exposed to higher concentrations of house dust mite, but no other associations with other definitions of eczema or exposure to cat allergen. This study extends the exposure-response analysis of allergen exposure to eczema outcomes measured up to age eight and also investigated the role of other genetic and environmental determinants.

Methods: 593 children (92.4% of those eligible) born to all newly pregnant women attending one of 3 GP surgeries in Ashford, Kent, were followed up from birth to age eight. Concentrations of house dust mite and cat allergen were measured in dust samples collected from the home eight weeks after birth. The risk of subsequent eczema as defined by the UK diagnostic criteria was determined according to different levels (quintiles) of allergen exposure at birth.

Results: By age eight, 150 (25.3%) children had met the diagnostic criteria for eczema at least once. Visible flexural dermatitis was recorded at least once for 129 (28.0%). As in other studies, parental allergic history was positively associated with most eczema outcomes, and higher maternal education and less crowded homes were associated with increased risk. No clear linear association between early exposure to house dust mite and cat allergen were found, regardless of the definition of eczema used. The risk of eczema appeared to increase for the three lowest quintiles of house dust mite allergen exposure (OR 1.37 for 3rd quintile compared with first), and then fall for the two highest quintiles (OR 0.66 and 0.71) even after controlling for confounding factors.

Conclusions: The lack of any clear exposure-disease relationship between allergens in early life and subsequent eczema argues against allergen exposure as being a major determinant of eczema incidence. If our data suggesting that there may be a reduced risk of eczema at higher levels of house dust mite is true, then interventions aimed at reducing house dust mite in early infancy could paradoxically increase the risk of subsequent eczema.

[377 words]

Introduction

The prevalence of atopic eczema (synonym "atopic dermatitis" or "eczema" using the World Allergy Association new nomenclature) [1] in children in the UK has been estimated between 14% and 20% [2-4] but little is known about its causes. There is little published material concerning cat exposure and childhood eczema. In a large study of 35,552 Japanese schoolchildren, current cat ownership was found to be related to a significantly lower prevalence of atopic dermatitis [5].

The role of house dust mite aeroallergens in initiation and continuation of eczema has been proposed for some time although results are inconclusive. In a recent review [6] the authors stated "The fact that patients with atopic eczema/dermatitis syndrome react consistently to dust mites supports the view that mite exposure is a major cause of the disease".

Earlier studies of house dust mite exposure and childhood eczema tended to be uncontrolled studies, where patients have been removed from their usual environments. Many reported improvements in symptoms [7-12] although the one study which also measured allergen exposure [10] found no correlation between changes in eczema severity and changes in house dust mite exposure.

A number of randomized controlled trials have been conducted, usually by comparing a placebo group with an active mite avoidance group. Mite avoidance was achieved by the use of mattress covers, frequent cleaning of bedrooms and other measures. Four such studies [13-17] reported significant associations between allergen avoidance and reduction in symptoms. Two further trials [18;19] demonstrated improvement in symptoms but little evidence that this could be directly related to Der p1 concentrations. In a trial of feeding practices amongst high risk infants [20], although modification of mite exposure was not incorporated into the design of the study, dust samples were collected, and house dust mite exposure was not associated with eczema at age one. The most recently reported trials have been larger and associations less convincing; three randomized birth cohort studies [21-23] have both failed to demonstrate associations between mite avoidance and childhood eczema. There are few reported observational studies. One study from Taiwan [24] of 931 healthy newborns reported a significantly higher incidence of atopic dermatitis at age 3 amongst children exposed to ≥1 μg/g house dust mite (21.6%) compared to those exposed to <1 μg/g (5.3%; p=0.0156).

In contrast, in an earlier publication from a UK birth cohort we reported a protective role of higher house dust mite exposure amongst children with parentally-reported doctor diagnosed eczema by age two [2] although there were no other associations between house

dust mite or cat allergen exposure and other measures of eczema by age two. One possible reason for such a lack of association was the reliance on parental report of diagnosed eczema.

Recently we have also reported findings from this birth cohort in relation to exposure to house dust mite and cat allergens in early life and subsequent atopy, wheeze and atopic wheeze at age 5½ [25]. We found no clear linear association between early life exposure to house dust mite or cat allergen and these outcomes; the exposure-response associations appeared to rise steeply at low levels of exposure and become attenuated at higher levels of exposure. Alongside these allergic respiratory symptoms we have collected a data on eczema as defined by the full UK diagnostic criteria as well as visible flexural eczema for these cohort children up to age eight, and here report the extension of the exposure-response analyses to these outcomes.

Methods

Assembly of birth cohort

Recruitment to the birth cohort commenced in November 1993. All newly-pregnant women presenting at one of three GP surgeries in Ashford, Kent, for antenatal care were approached to join. A total of 710 were approached and 658 (93%) agreed to participate. At recruitment, all but three of the mothers and 542 (87%) of their partners underwent skin prick tests to three common allergens (*Dermataphagoides pteronyssinus*, cat fur and mixed grass pollens; Allergopharma [Hamburg, Germany]). An adult was considered to be atopic if at least one mean weal was at least 3mm greater than the negative (saline) control. Also at this stage, information on family size and other lifestyle factors were collected, including occupational details necessary for allocating social class according to the Registrar General's 1990 classification. A total of 642 babies were born. Children were visited annually from birth until they were aged eight and details on various aspects of their health over the preceding 12 months were collected by questionnaires administered to a parent.

Dust sampling

Approximately eight weeks after birth each baby was visited at home and dust samples were collected from the living room floor. These samples were assayed for concentrations of house dust mite and cat allergen using standard techniques as described previously [26]. These exposure measurements were available for 624 (97%) of the cohort children.

Definitions of eczema used

Questions regarding the dryness of the child's skin and other features of atopic eczema were asked at all annual visits, and an examination of each child for evidence of visible flexural dermatitis as per photographic protocol (ref http://www.nottingham.ac.uk/dermatology/eczema/index.html) was completed where possible. A child was considered to have eczema if they experienced an itchy skin in the past twelve months plus at least three of the following; a history of flexural involvement, history of a generally dry skin, history of allergic disease in parents or siblings and visible dermatitis as per photographic protocol. In this way, we could estimate annual point prevalence of eczema according to the UK criteria and visible dermatitis, and calculate the proportion of children who had ever met these criteria, or had visible dermatitis. Data up to age eight was available for 593 (92.4%) of cohort children.

At ages 5½ and eight, skin tests were performed on the children, when consent from both the parent and the child was obtained. Atopy was defined as at least one mean weal (names, ALK) at least 2mm greater than the negative (saline) control. Skin tests were performed on 552 (86.0%) and 548 (85.4%) children at each occasion. Atopic children who ever had eczema according to the UK criteria or visible dermatitis were considered as separate primary outcomes of interest.

Secondary outcomes of interest were maternally-reported eczema by age eight, and maternal recall of whether their family practitioner had ever diagnosed eczema by age eight. Finally, all available medical records (n=594; 92.5%) were reviewed at ages three, six and eight by the research nurses and a documented diagnosis, or query diagnosis of eczema was recorded.

The study was approved by the local ethics committee and a parent or guardian of each participant provided informed consent.

Statistical analysis

Allergen concentrations were categorized into quintiles of equal size. Comparisons between exposure quintiles and subsequent measures of eczema were computed using chi-squared tests for trend. Logistic regression techniques were used to quantify independent determinants of the eczema outcomes. A forward stepwise procedure was implemented for each outcome with the exposure measurements forced into each model. Likelihood ratio tests were used to estimate the contribution made to the model for each determinant. A

range of determinants were considered, and all with a p-value <0.25 from univariate analysis were individually entered into the base model. The factor with the smallest p-value (<0.15) arising from the likelihood ratio tests was then added to the model. This procedure was repeated for all considered determinants until there were no more with p<0.15. All analyses were completed using SAS (NC, Cary, USA) and Stata (College Station, Texas, USA).

Results

Prevalence of eczema

By age eight, 150 (25.3%) children had met the diagnostic criteria for eczema at least once, with annual point prevalence lying between 8.3% and 10.6% (Figure 1). Of those with sufficient skin test information (n=533; 83.0%), 130 (24.4%) were atopic. Fifty children (8.7% of cohort; 33.3% of those with eczema) were atopic and met the UK diagnostic criteria for eczema. Point prevalence of visible flexural dermatitis varied between 4.8% and 7.1% (Figure 1) with a positive identification occurring at least once for 129 (28.0%) children. Of these 129 children, most had visible dermatitis observed on only one annual visit (n=84; 65.1%) or two visits (n=25; 19.4%) and only two children (1.6%) had visible flexural dermatitis each time they were examined up to age 8.

Of the 150 children with eczema at some point by age eight, 85 (56.7%) were identified by age two and 65 (43.3%) after age two. Almost half (43.2%) of the children with eczema by age two were atopic at either skin test and 18 (32.7%) of those with eczema identified later were atopic. Many of the children with eczema identified by age two also had eczema at later ages (n=58; 68.2%). Sixty nine children (55.6%) with visible flexural dermatitis which was witnessed by the research nurses at the time of their visits at age one or two; 55 (44.4%) had their flexural dermatitis at least once between the ages of two and eight, and not before the age of two. Very little missing data for visible flexural dermatitis exists for children seen at home up to age 4 (maximum 2.9%) but as the visits at ages 5½ and 8 were conducted at school some missing data exists (9.0% and 5.8% respectively).

Parents of over half of the children (n=375; 61.9%) felt that their child had had eczema at some point before their eighth birthday and 328 (54.7%) reported receiving a doctor's diagnosis. This figure was similar to the number of children who received a diagnosis of eczema, or query eczema, which was recorded on their notes (n=312; 52.5%). Agreement between the parentally-reported diagnoses and actual recorded diagnosis was 78%, with a similar number of children for whom the parents reported having had a diagnosis where

none was recorded (n=72) as children whose parents did not report having a diagnosis where one was recorded in the medical notes (n=60).

Of those children whose parents believed had eczema, most reported this before age two (283; 75.5%). Over half of the parents who reported a doctor's diagnosis of eczema reported this before age two (193; 58.8%) and a diagnosis of eczema or query eczema was likely to be recorded in the child's medical notes before age two (222; 71.2%).

Exposure-response associations

The observed associations between house dust mite quintiles and eczema prevalence were clearly non-linear (Figure 2); the rates of eczema according to the UK criteria by age eight rose for lower levels of exposure but reduced for higher levels. This pattern was also observed for the other primary outcomes of interest of eczema according to the UK criteria with atopy, visible flexural dermatitis and visble flexural dermatitis with atopy. Similar patterns were observed for the three secondary outcomes with non-significant associations (data not shown; p_{trend} = 0.21 for doctor-diagnosed eczema, 0.34 for parentally-reported doctor-diagnosed eczema and 0.67 for parental opinion of eczema).

The associations between cat allergen quintiles and the main outcomes were also not linear (Figure 3); broadly following similar patterns as found for house dust mite. Again, these were replicated for the secondary outcomes (data not shown; p_{trend} = 0.41 for doctor-diagnosed eczema, 0.91 for parentally-reported doctor-diagnosed eczema and 0.47 for parental opinion of eczema).

For each exposure, similar findings were observed when the outcomes were restricted to children who were sensitized to that allergen: house dust mite exposure quintiles *versus* house dust mite-sensitized children with eczema (n=29; data not shown; p_{trend} = 0.89) and cat allergen exposures *versus* cat-sensitized children with eczema (n=32; data not shown; p_{trend} = 0.16).

Multivariate modeling

In only one adjusted model did the association between exposure to aeroallergens in early life and eczema approach statistical significance (Table 2; cat allergen exposure and the risk of visible flexural dermatitis with atopy; p=0.08) although there was little evidence that this pattern was linear (p=0.58 if the term was included as a linear term). In all other models (Tables 1 and 2) there was no evidence to suggest any clear exposure-response association between domestic aeroallergen exposure and subsequent eczema.

There were some other findings of interest; the risk of eczema according to the UK criteria increased with maternal history of allergic disease, paternal atopy and paternal age (Table 1). Maternal history of allergic disease and paternal atopy were also associated with increased risk of eczema with atopy, along with increased risk observed for children with mothers of higher educational experience and less crowded homes. Mothers with higher numbers of years in education were also more likely to have children with flexural dermatitis (Table 2; p=0.03) with maternal and paternal history of allergic disease and a less crowded home also positively associated with visible flexural dermatitis. Males were significantly less likely to have visible flexural dermatitis (OR 0.59, 95% ci [0.38, 0.91]; p=0.02). When analysis was restricted to those who were also atopic, the only factor which remained significant was the low crowding index (OR 4.40 [2.23, 8.70]; p<0.001).

The results from the three secondary outcomes were similar both in respect to non-linear exposure-response associations and specific risk factors (data not shown). Maternal allergy and/or paternal atopy were significantly associated with increased risk of each secondary eczema outcome and there was evidence of increased risk with decreased crowding, higher social class, and increased maternal education.

Discussion

We have failed to find any clear linear association between house dust mite or cat allergen exposure quantified in early life and subsequent eczema, measured in a variety of ways. More convincing associations were found for genetic factors and environmental influences. One adjusted model did demonstrate a borderline significant association between cat allergen exposure and the risk of visible flexural dermatitis with atopy; however this association was clearly non-linear, with the highest prevalence recorded for the second lowest exposure category.

Other findings were similar to our previous report [2] where parental history of allergic disease and parental atopy were associated with the measures of eczema. As before, we also found some evidence of increased prevalence amongst children whose mothers had stayed in education longer, and for children from less crowded homes. These findings support earlier reports of increasing prevalence of eczema amongst more advantaged social groups [27]. One surprising finding was the protective effect of smoking during pregnancy upon a recorded diagnosis of eczema in the medical notes. A possible explanation for this finding may be that this is simply a reflection of attendance at GP surgeries. **(omit?)**

Our reported prevalence of eczema was similar to other studies. Findings from a large cohort study recently reported period prevalence of 21.0%, 25.6%, 23.2% and 19.9% at six, 18, 30 and 42 months respectively [28]. Another study using the same cohort reported visible eczema at age 5 was seen in 12.2% children [29]. A one-year prevalence of 11.5% and cumulative incidence of 20% was reported among primary school children aged between three and 11 years in 1989 in Birmingham [3]. Shamssain *et al.* [30] reported a cumulative incidence of 27.8% in NE England amongst children aged 6-7.

Although many controlled and uncontrolled studies have shown associations between house dust mite avoidance and eczema [7-17;24], the ability to directly relate this to house dust mite exposure has been limited [10;18;19]. Our findings are in agreement with our earlier report [2] and more recent, larger, randomized birth cohort studies [21-23]. The shape of the exposure-response associations described here are also consistent with those previously reported for sensitization and wheeze at age 5½ [25] with a tendency for reduced risk in the higher exposure quintiles. Although the confidence intervals for the higher quintiles overlap, this finding was consistent across different measures of eczema.

Although not a particularly large cohort, this data is mostly complete and likely to be representative. The cohort was assembled by approaching all women seeking antenatal care irrespective of allergic history and the recruitment and retention rates were very high. There was no evidence in this cohort that exposures to house dust mite or cat allergen were different with an allergic parent or sibling so it is unlikely that behavioural factors have biased these results.

Our study findings demonstrate that allergen exposure is not associated with subsequent eczema amongst children. Previous advice provided by investigators regarding the use of bedcovers and other allergen avoidance methods is unlikely to have much impact upon the prevalence of eczema in childhood. The reported findings of increased risk associated with higher maternal education and less crowded homes may be consistent with the concept that different early life exposures to some environmental agents increase risk of allergic disease.

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Table 1: Determinants of eczema by UK criteria derived from logistic regression

	eczema by UK criteria *(n=150)*			eczema by UK criteria + atopy *(n=50)*		
	n (%)	adjusted* OR (95% ci)	p	n (%)	adjusted OR (95% ci)	p
Maternal allergy -	70 (20.4%)	1.00	0.001	20 (6.0%)	1.00	0.01
+	80 (32.1%)	1.95 (1.30, 2.93)		30 (12.6%)	2.44 (1.22, 4.88)	
Paternal atopy -	69 (22.1%)	1.00	0.02	23 (7.5%)	1.00	0.05
+	68 (30.6%)	1.64 (1.09, 2.47)		23 (11.0%)	1.99 (0.99, 3.99)	
Crowding index high		--		28 (6.0%)	1.00	0.01
low				22 (20.6%)	2.75 (1.31, 5.78)	
Maternal education beyond age 16:						
none		--		12 (5.3%)	1.00	0.04
< 2 years				16 (7.8%)	1.25 (0.51, 3.05)	
≥ 2 years				20 (14.9%)	2.84 (1.17, 9.89)	
Paternal age		1.04 (1.01, 1.09)	0.03		--	
Quintile of house dust mite exposure:						
1	27 (23.5%)	1.00	0.15	8 (7.1%)	1.00	0.33
2	32 (27.6%)	1.01 (0.53, 1.92)		11 (10.0%)	0.94 (0.32, 2.72)	
3	37 (31.6%)	1.37 (0.74, 2.55)		15 (13.2%)	1.87 (0.69, 5.03)	
4	23 (19.2%)	0.66 (0.34, 1.29)		7 (6.0%)	0.74 (0.23, 2.35)	
5	27 (23.1%)	0.71 (0.37, 1.37)		7 (6.2%)	0.68 (0.21, 2.18)	
Quintile of cat allergen exposure:						
1	22 (19.8%)	1.00	0.84	5 (4.5%)	1.00	0.15
2	35 (29.4%)	1.42 (0.72, 2.81)		12 (10.5%)	4.03 (1.02, 15.90)	
3	30 (25.2%)	1.41 (0.71, 2.79)		10 (8.7%)	3.05 (0.74, 12.57)	
4	27 (23.7%)	1.31 (0.65, 2.62)		13 (11.9%)	4.37 (1.09, 17.45)	
5	33 (27.1%)	1.41 (0.72, 2.75)		9 (7.6%)	2.18 (0.53, 8.99)	

**only terms which met the necessary level of significance were included in the final model; all terms in this final model are adjusted for all others included*

Table 2: Determinants of visible flexural dermatitis derived from logistic regression

	visible flexural dermatitis *(n=129)*			visible flexural dermatitis + atopy *(n=46)*		
	n (%)	adjusted* OR (95% ci)	p	n (%)	adjusted OR (95% ci)	p
Maternal allergy -	65 (24.3%)	1.00	0.03		--	
+	64 (33.0%)	1.61 (1.04, 2.50)				
Paternal allergy -	82 (30.2%)	1.00	0.08		--	
+	44 (24.0%)	0.67 (0.43, 1.05)				
crowding index high	97 (25.6%)	1.00	0.15	27 (6.2%)	1.00	<0.001
low	32 (39.0%)	1.52 (0.87, 2.64)		19 (20.4%)	4.40 (2.23, 8.70)	
Maternal education beyond age 16:						
none	40 (21.6%)	1.00	0.03		--	
< 2 years	47 (28.3%)	1.32 (0.79, 2.21				
≥ 2 years	39 (36.5%)	2.17 (1.22, 3.88)				
Sex F	65 (33.7%)	1.00	0.02		--	
M	64 (23.9%)	0.59 (0.38, 0.91)				
Quintile of house dust mite exposure:						
1	22 (25.9%)	1.00	0.32	6 (5.8%)	1.00	0.32
2	27 (30.0%)	1.17 (0.58, 2.34)		13 (13.0%)	2.53 (0.90, 7.13)	
3	30 (34.5%)	1.73 (0.87, 3.46)		12 (11.4%)	2.16 (0.76, 6.20)	
4	23 (24.7%)	0.88 (0.43, 1.81)		8 (7.7%)	1.51 (0.49, 4.65)	
5	26 (25.2%)	0.96 (0.47, 1.94)		6 (5.5%)	1.18 (0.36, 3.90)	
Quintile of cat allergen exposure:						
1	22 (25.6%)	1.00	0.61	6 (5.9%)	1.00	0.08
2	30 (32.6%)	1.28 (0.64, 2.56)		14 (13.7%)	2.93 (1.04, 8.23)	
3	22 (23.4%)	0.75 (0.36, 1.55)		6 (5.6%)	0.86 (0.26, 2.85)	
4	28 (30.8%)	1.18 (0.59, 2.38)		12 (12.1%)	1.76 (0.60, 5.15)	
5	27 (28.1%)	0.96 (0.48, 1.91)		8 (7.1%)	1.03 (0.33, 3.18)	

**only terms which met the necessary level of significance were included in the final model; all terms in this final model are adjusted for all others included*

Figure 1: Annual point prevalence of eczema according to UK diagnostic criteria and visible dermatitis

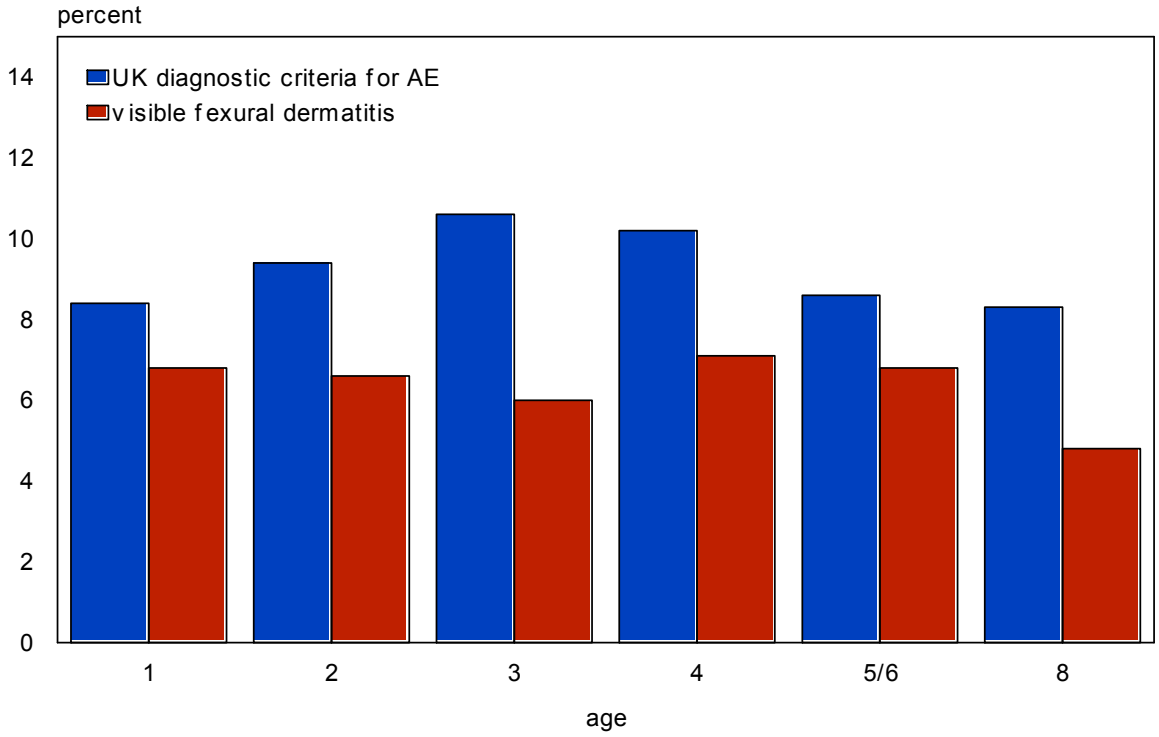

Figure 2: House dust mite exposure quintiles and primary eczema outcomes

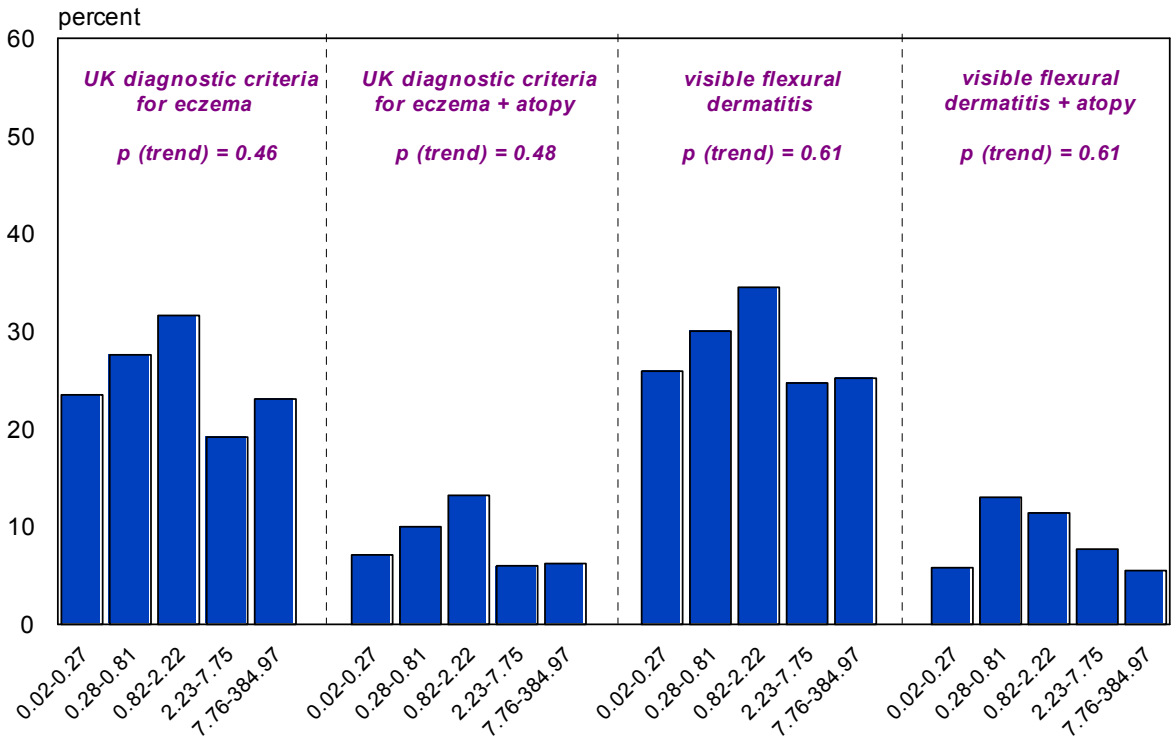

Figure 3: Cat allergen exposure quintiles and primary eczema outcomes